Urban air pollution and chronic obstructive pulmonary disease-related emergency department visits

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ABSTRACT

Background: Patients with chronic obstructive pulmonary disease (COPD) can have recurrent disease exacerbations triggered by several factors, including air pollution. Visits to the emergency respiratory department can be a direct result of short-term exposure to air pollution. The aim of this study was to investigate the relationship between the daily number of COPD emergency department visits and the daily environmental air concentrations of PM_{10}, SO_2, NO_2, CO and O_3 in the City of São Paulo, Brazil.

Methods: The sample data were collected between 2001 and 2003 and are categorised by gender and age. Generalised linear Poisson regression models were adopted to control for both short- and long-term seasonal changes as well as for temperature and relative humidity. The non-linear dependencies were controlled using a natural cubic spline function. Third-degree polynomial distributed lag models were adopted to estimate both lag structures and the cumulative effects of air pollutants.

Results: PM_{10} and SO_2 readings showed both acute and lagged effects on COPD emergency department visits. Interquartile range increases in their concentration (28.3 $\mu g/m^3$ and 7.8 $\mu g/m^3$, respectively) were associated with a cumulative 6-day increase of 19% and 16% in COPD admissions, respectively. An effect on women was observed at lag 0, and among the elderly the lag period was noted to be longer. Increases in CO concentration showed impacts in the female and elderly groups. NO_2 and O_3 presented mild effects on the elderly and in women, respectively.

Conclusion: These results indicate that air pollution affects health in a gender- and age-specific manner and should be considered a relevant risk factor that exacerbates COPD in urban environments.

Chronic obstructive pulmonary disease (COPD) is a major and increasingly prevalent global health problem. It is predicted to become the third most common cause of death and the fifth most common cause of disability globally by 2020.[1] According to World Health Organization (WHO) estimates, approximately 80 million people have moderate to severe COPD and 3 million died of COPD in 2005, equivalent to 5% of all deaths globally.[2] The Global initiative for chronic Obstructive Lung Disease (GOLD) has adopted a new definition for COPD, which recognises airflow limitations as often being progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases.[1] This definition suggests that COPD is a chronic inflammatory disease, and, in that sense, most recent studies have been in accordance with this notion.

In developed countries, cigarette smoking is by far the most common cause of COPD cases. Notwithstanding, there are other risk factors including indoor air pollution from fuel burning, poor diet and occupational exposure.[2] Patients with COPD may have recurrent exacerbations, with symptoms worsening and reduction in lung function that may not be recovered. Moreover, COPD exacerbations result in an impaired quality of life, reduced survival rate and increased healthcare costs.[3]

In the last few decades, atmospheric pollution has been identified as a cause of COPD exacerbations.[4 5] Once in contact with the respiratory epithelium, pollutants can activate an inflammatory cascade that results in damage to that tissue. The relationship between diesel particulates, sulphur dioxide (SO_2), ozone (O_3) and nitrogen dioxide (NO_2) and respiratory inflammation has also been demonstrated.[6 7] Seaton and colleagues[8] suggest that the deposition of particles in the lung provokes low-grade alveolar inflammation that causes COPD exacerbations. Emergency department (ED) visits related to COPD have been accepted as a sensitive outcome of the short-term effects of air pollution,[9] an association that is supported by other epidemiologic studies.[10–14]

In São Paulo, one of the world's most densely populated cities (11.2 million inhabitants), the main source of air pollution is lightweight cars that run on a petrol–ethanol mixture, resulting in the emission of pollutants with a single toxic component. In São Paulo, the prevalence of COPD reaches 19.8% among men over 40 and 14.5% among women over 40.[15] In addition, adult smoking rates for men and women in the city are around 23% and 17%, respectively.[16]

Owing to the prevalence of COPD as a health problem among adults and the elderly in São Paulo and permanent exposure to pollutants, the aim of this study was to estimate the impact of daily air pollution variability on COPD exacerbation rates, measured via records of daily ED visits.

MATERIALS AND METHODS

We conducted an ecological time-series study. Daily records of COPD ED visits for patients older than 40 were obtained from São Paulo Hospital (SPH), an affiliate of the São Paulo Federal University, from 1 February 2001 to 31 December

2003. The COPD cases were defined based on criteria in the International Classification of Diseases (ICD) 10th revision and took into consideration the primary diagnosis in each ED visit record. Patients with bronchitis (J40, J41 and J42), emphysema (J43) and other COPDs (J44) were included in the study. The SPH is an accredited teaching hospital and its ED treats approximately 50 000 patients per year. It has, therefore, been used as a sentinel health service centre for epidemiological studies that aim to evaluate the relationship between air pollution and respiratory morbidity.

Daily records of particulate matter with an aerodynamic profile $\leqslant 10$ μm (PM_{10}), carbon monoxide (CO), SO_2, O_3 and NO_2 were obtained for the entire analysis period from the São Paulo State Environmental Agency. Thirteen monitoring stations are distributed throughout the city. For each measured pollutant, the average value among stations was adopted as an estimate of city-wide exposure rates. The measurement adopted for CO (non-dispersive infrared) showed the highest 8 h moving average at five stations. For NO_2 (chemiluminescence) and O_3 (ultraviolet), the highest hourly average was measured at four stations. The highest hourly average over a 24 h period for PM_{10} (beta radiation) was measured at 12 stations and at 13 stations for SO_2 (pulse fluorescence—ultraviolet); 24 h averages were adopted. Small volumes of missing data were replaced by centred moving averages. All pollutants were measured from 00:01 to 00:00. Daily minimum temperatures and daily means of relative air humidity were obtained from the Institute of Astronomy and Geophysics at the University of São Paulo.

The correlations between pollutants and weather variables were estimated using Pearson or Spearman correlation coefficients. The daily number of COPD ED visits was the dependent variable. The independent variables were the daily mean levels of each pollutant (PM_{10}, SO_2, CO, NO_2 and O_3). We also controlled for short-term (ie, days of week) and for long-term (ie, seasonable) and daily climate conditions (minimum temperature and humidity). Counts of daily COPD ED visits were modelled, for the entire period, using generalised linear Poisson regressions.[17] Analysis was stratified by gender and age (ages 40–64 and older than 64). A Poisson regression model was adopted because ED visits are countable events that exhibit a Poisson distribution. We used natural cubic splines[18] to control for season. Splines were used to account for the non-linear dependence of ED visits on that covariate and to subtract the basic seasonal patterns (and long-term trends) from the data. We used 12 degrees of freedom to smooth the time trend. The number of degrees of freedom for the natural spline of the time trend was selected to minimise the autocorrelation between the residuals and the Akaike Information Criterion.[19] After adjusting for the time trend, no remaining serial correlation was found in the residuals, making the use of autoregressive terms unnecessary.

Indicators for day of the week were included in order to control for short-term trends. Respiratory diseases present a nearly linear relationship with weather. Linear terms for temperature and relative humidity were therefore adopted. Effects of minimum temperature were more relevant from lag 0 to lag 2. Hence, we adopted a 3-day moving average for the minimum temperature. Relative humidity exhibited a short-duration and small-magnitude effect on COPD admissions. We adopted a 2-day moving average for relative humidity. To reduce sensitivity to outliers in the dependent variable, we used robust regression (M-estimation).

The lag structures between air pollution and health were analysed using different approaches and time lags. In this study, we tested the lag from the same day to 6 days before the ED visit using a third-degree polynomial distributed lag model.[18] Although this imposes constraints, it also allows for sufficient flexibility to estimate a biologically plausible lag structure that controls for better multicollinearity than an unconstrained lag model. The standard errors of the estimates for each day were adjusted for overdispersion. After defining the lag structure for criteria pollutants, we estimated the cumulative effects of 2, 3 and 6 days.

Effects of air pollutants were expressed as a percentage increase and as 95% confidence intervals (95% CIs) in COPD-related ED visits. This was due to increases in pollutant concentrations of a magnitude equal to that of the interquartile range (ie, the variation between the 75% higher and the 25% lower daily concentrations). All analyses were performed using the S-Plus 2000 statistical package for Windows.

RESULTS

During the study, 48 109 patients with respiratory diseases were examined. A total of 9443 were over 40 and 1769 were classified as having COPD. The descriptive analyses of COPD events are shown in table 1.

As shown in table 1, COPD-related ED visits were infrequent during the study period. The daily mean number of total COPD visits, however, increased annually in the 3-year period (2001, 1.34 $\pm$1.48; 2002, 1.54 $\pm$1.16; and 2003, 1.78 $\pm$1.53).

Table 2 presents a description of air pollutants and weather variables.

On average, the pollutants remained below their respective air quality guideline limits on most of the observed days (fig 1). The PM_{10} daily level, however, exceeded its limit (150 $\mu g/m^3$) once. The NO_2 daily limit (100 $\mu g/m^3$) was exceeded several times, the CO 8 h moving average was exceeded four times and the 1 h O_3 maximum was exceeded 54 times. Records for SO_2 across the entire period, the NO_2 and O_3 annual means increased from the first to the last year of the study.

Primary pollutants showed high positive correlations (Pearson or Spearman correlations): PM_{10} and CO, 0.67; PM_{10} and SO_2, 0.77; PM_{10} and NO_2, 0.60; SO_2 and CO, 0.52; SO_2 and NO_2, 0.63; NO_2 and CO, 0.56. Furthermore, COPD showed positive and significant correlations with primary pollutants but not with O_3.

Table 3 shows the lag structure of PM_{10}, SO_2 and CO effects on COPD-related ED visits for total, gender-specific and age-specific groups.

Across the entire group, COPD exacerbations increased on the same day that PM_{10} increased (lag 0) and the effects decreased during the subsequent 5 days. This pattern was observed in all adults, but was only significantly different in the elderly group, in which a positive effect was observed at a 5-day lag. The cumulative effects were significant and, for the elderly group, the highest effect was almost double the values obtained in younger adults.

The patterns of lag structure for SO_2 across all groups were similar to those observed for PM_{10}. Furthermore, the magnitudes of the effects were similar to PM_{10} values, with the exception of the magnitudes observed in the elderly group. Among the elderly, the length of the effect lag was longer than that observed in younger adults.

Interquartile range increases in CO presented a different pattern of lag structure when compared with PM_{10} and SO_2. For the entire group, COPD-related ED visits increased 2 days after air pollution increases, thereby showing a cumulative effect that lasted 7 days. The same pattern was observed for men, women

Table 1 Description of emergency department (ED) visits for chronic obstructive pulmonary disease (COPD)

COPD-related ED visits	Number	Mean	SD	Minimum	Maximum
Women					
40–64	496	0.47	0.79	0	5
>64	298	0.28	0.57	0	3
Total	794	0.75	1.04	0	7
Men					
40–64	484	0.45	0.74	0	4
>64	491	0.46	0.7	0	4
Total	875	0.92	1.05	0	6
Total 40–64	980	0.92	1.16	0	6
Total >64	789	0.74	0.94	0	6
Total	1769	1.66	1.62	0	10

and the elderly. For the adults, despite the smaller magnitude of the effects, increases in COPD-related ED visits were observed the day after a CO increase and remained elevated for 3 days thereafter.

The effects of NO_2 and O_3 were not nearly as significant as those observed for PM_{10}, SO_2 and CO. The NO_2 levels affected only COPD-related ED visits among the elderly. This effect was delayed (at lag 5 with an increase of 7.8%, 95% CI 0.8 to 15.3) and a 6-day cumulative effect of significant magnitude was also observed (17.8%, 95% CI 0.3 to 38.3). Ozone presented a small and acute effect (lag 0) for women (2.3%, 95% CI 0.0 to 4.5) but had no impact on the other groups.

DISCUSSION

This time-series study of COPD-related ED visits provides a rare opportunity to examine associations between an extensive collection of ambient pollutant measures and COPD exacerbation rates. PM_{10}, SO_2 and CO were associated with outcomes using a gender- and age-stratified group analysis. The study ultimately concluded that NO_2 and O_3 presented group-specific effects for elderly people and women, respectively.

Time-series analysis is widely used to assess the association between air pollution and acute respiratory health outcomes. Although having the advantage of controlling for temporal trends in the data, time-series analysis is also associated with certain disadvantages. Results from time-series analyses are model dependent.[20] Some authors have recently chosen to use case-crossover analyses to estimate the acute effects of air pollution. However, the results have shown that case-crossover and time-series techniques, when adequately performed, produce quite similar estimates.[20] The adoption of generalised linear models in our study should, therefore, not be considered a weakness of this work.

There is no general agreement regarding the definition of COPD exacerbation. It can be defined based on increasing symptoms and/or increasing utilisation of healthcare services,[21] and it is characterised by an intense inflammatory process in the airways, parenchyma and pulmonary vasculature.[1] Exacerbations are brought on or triggered by a variety of factors, the most important of which are respiratory infections, air pollution and temperature. Furthermore, COPD exacerbations are associated with the worsening of pre-existing (acute-on-chronic) respiratory inflammation.[22] Certain other clinical manifestations include fatigue in respiratory muscles, leading to ventilatory pump failure, hypercapnia and respiratory insufficiency.[22]

Strong epidemiological evidence has shown that air pollution can adversely affect patients with COPD. The adverse impact also seems to be modulated by different characteristics.[23] Among those effect modification factors, gender and age are the most relevant.[24–26] The severity of COPD is higher among women than among men.[24 25] These characteristics may explain the differences in COPD mortality that are associated with air pollution exposure among elderly people, and that appear with higher incidence among women.[24 25]

Women are known to present more pronounced airway responsiveness than men. This characteristic has been linked to their increased susceptibility to environmental pollutants.[26] Moreover, the smaller diameter of the airways and the lower anatomical dead space volume in the lungs of women enhances the deposition of particles in the lower airways.[25] Different from men, in whom the first manifestation of COPD exacerbation are increases in cough and sputum, the first manifestation in women can be associated with changes in lung function.

Particulates can induce oxidative stress and inflammatory responses in the airways. There is empirical evidence and experimental support showing that direct damage to the respiratory mucosa (ie, increased permeability and reduced mucociliary activity) is a result of oxidative damage and secondary toxic effects mediated by proinflammatory cytokines.[27–29] By the

Table 2 Summary of environmental (pollutants and weather) variables

					Percentiles		
Variables	Daily mean	SD	Minimum	Maximum	25th	50th	75th
CO (ppm)	2.71	1.23	1.00	12.00	1.90	2.50	3.20
O_3 ($\mu g/m^3$)	95.75	44.24	14.50	282.00	63.85	88.65	119.70
NO_2 ($\mu g/m^3$)	120.34	49.86	30.90	390.80	81.75	113.80	150.20
SO_2 ($\mu g/m^3$)	14.00	6.15	2.10	42.90	9.60	13.20	17.40
PM_{10} ($\mu g/m^3$)	48.71	21.87	9.60	169.00	32.30	43.90	60.60
Minimum temperature (°C)	15.50	3.37	3.70	21.80	13.10	15.80	18.20
Mean relative humidity (%)	79.17	8.43	45.50	96.60	74.50	80.00	85.00

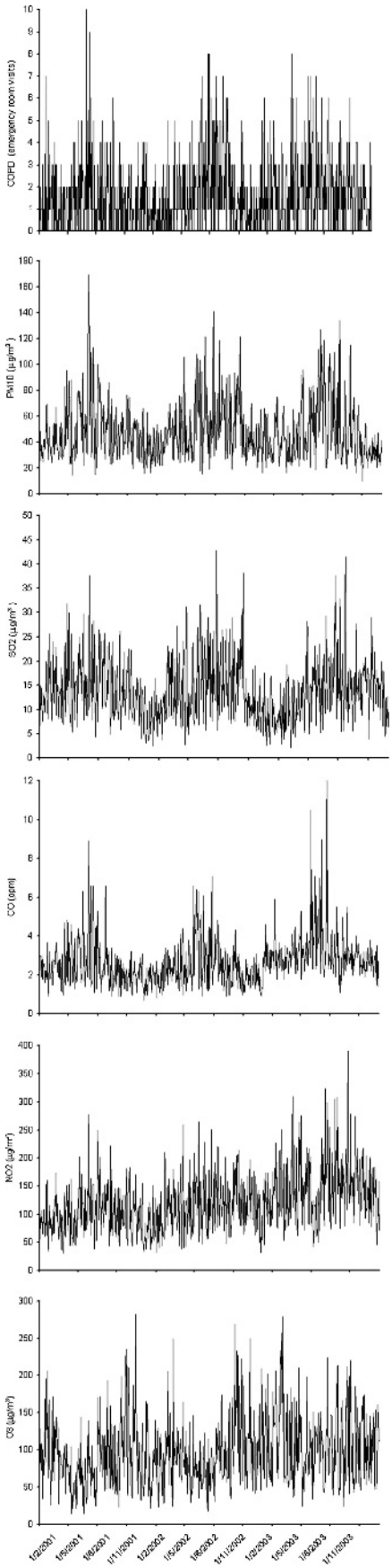

Figure 1 Daily records of chronic obstructive pulmonary disease-related emergency department visits and air pollutants in São Paulo from 2001 to 2003.

same token, the characteristic oronasal breathing pattern of patients with COPD might play a role since there is a deeper deposition of particles in the lower respiratory tract. Patients with COPD who tend to breathe orally appear to experience a remarkable increase in pulmonary particle deposition.[30]

SO_2 is a gas produced by fuel combustion. Currently, the major source of combustion pollution in most cities is traffic. Hence, SO_2 might be a surrogate of the traffic pollution mixture. SO_2 is a highly reactive gas whose concentration is very seasonal, peaking in the winter.[11] Current biological knowledge suggests that SO_2 can exacerbate COPD. In animals, low and short-term SO_2 exposures accelerate mucociliary clearance by reflex mechanisms, as suggested by increases in secretion rates of mucus.[31] In human-related studies, SO_2 has been associated with bronchoconstriction in normal and sensitive subjects after short-term (5 min) exposures.[32] With this in mind, the current knowledge data from the toxicological and biological fields suggest that SO_2 can exacerbate COPD. Owing to the strong interactions between particulate matter and SO_2, Bascon *et al*[33] suggested that the health effects of particles, SO_2 and acid aerosols must be jointly evaluated. In our study, the high correlation observed between PM_{10} and SO_2 and their similar effect patterns support the recommendation by Bascon *et al*.

COPD is now recognized as a systemic disorder which includes extrapulmonary manifestations, such as skeletal muscle dysfunction and muscle wasting.[34] Reduction of peripheral muscle strength occurs during acute COPD exacerbations.[34] The toxic properties of CO are largely attributed to its high affinity for oxygen-carrying Fe^{2+}-haem proteins, such as haemoglobin and myoglobin (Mb), and the effects of CO exposure are often first manifested in the most oxygen-sensitive organ system.[35] Since CO competes with O_2 for Mb in cardiac and skeletal muscles, a decrease in blood arterial oxygen pressure (PaO_2) in such tissues will enhance carboxymyoglobin (COMb) formation, possibly causing CO to shift rapidly out of the blood (carboxyhemoglobin) into the muscle (COMb) compartment. Sequestration of Mb in the form of MbCO may limit the O_2 uptake rate by these tissues and impair oxygen delivery for intracellular contractile processes.[35] Carbon monoxide presented a lagged effect on COPD-related ED visits. Investigation of CO pathophysiology supports the hypothesis that exacerbations of COPD and consequent lagged ED visits associated with increased CO concentrations could be related to respiratory muscle dysfunction.

NO_2 has been associated with lung inflammation in smaller airways in normal subjects.[36] It can also lead to exacerbations of respiratory disease because of its capacity to impair the function of epithelial cells and alveolar macrophages.[37] As observed in our study and in the literature, however, findings regarding NO_2 effects are inconsistent owing to the difficulty in separating its effects from other co-pollutants.[38]

Ozone exposure compromises inspiration, which leads to immediate impairment of respiratory function with a reduction in forced vital capacity (FVC) and forced expiratory volume at 1 s (FEV_1), inflammation in the airways and increased bronchial responsiveness.[39] These characteristics support our findings in respect of the short-term effects of O_3 in women. The increased responsiveness of this group can be explained by the smaller size of female airways compared with male airways.[40] However, in spite of similar results observed in a few studies,[41 42] gender differences in the response to O_3 remain inconsistent.

Table 3 Percentage increases and 95% CIs for chronic obstructive pulmonary disease-related emergency department visits due to interquartile range increases in PM_{10} (28.3 μg/m³), SO_2 (7.8 μg/m³) and CO (1.3 ppm) according to gender and age

	Percentage increase (95% CI)				
	Total	**Male**	**Female**	**40–64 years**	**>64 years**
PM_{10}					
Lag 0	9.8 (1.0 to 19.3)	7.9 (−3.4 to 20.6)	13.6 (1.1 to 27.6)	10.4 (−1.2 to 23.3)	12.0 (−0.3 to 25.8)
Lag 1	1.7 (−2.7 to 6.3)	4.6 (−1.0 to 10.6)	−0.1 (−5.4 to 5.6)	3.7 (−1.8 to 9.7)	1.1 (−4.3 to 6.9)
Lag 2	−0.0 (−4.4 to 4.5)	3.2 (−2.99 to 9.6)	−3.3 (−9.0 to 2.7)	1.7 (−4.3 to 8.1)	−1.7 (−7.5 to 4.5)
Lag 3	0.1 (−3.1 to 3.5)	2.6 (−1.9 to 7.2)	−1.1 (−5.4 to 3.4)	1.7 (−2.7 to 6.3)	0.3 (−4.1 to 4.8)
Lag 4	3.2 (−1.3 to 7.8)	2.3 (−3.2 to 8.1)	0.3 (−5.6 to 6.6)	1.7 (−4.3 to 8.1)	4.3 (−1.8 to 10.9)
Lag 5	2.9 (−1.0, 6.9)	1.7 (−3.8, 7.5)	4.3 (−1.3, 10.3)	0.1 (−5.3, 5.8)	7.9 (2.1, 14.1)
Lag 6	−2.0 (−8.8 to 5.4)	0.3 (−8.7 to 10.2)	−0.6 (−10.0 to 9.9)	−5.2 (−14.2 to 4.7)	8.2 (−2.0 to 19.6)
S* 2 days	11.7 (1.6 to 22.7)	12.9 (−0.0 to 27.6)	13.5 (−0.1 to 28.9)	14.5 (1.4 to 29.4)	13.2 (−0.3 to 28.6)
S 3 days	11.6 (1.0 to 23.3)	16.5 (2.6 to 32.3)	9.7 (−4.5 to 26.0)	16.5 (2.0 to 33.0)	11.3 (−2.5 to 27.2)
S 6 days	18.6 (3.8 to 35.5)	24.3 (5.3 to 46.8)	13.5 (−4.9 to 35.5)	20.6 (1.6 to 43.2)	25.7 (5.9 to 49.2)
S 7 days	17.5 (−12.6 to 57.9)	24.7 (5.0 to 48.0)	12.9 (−5.5 to 34.7)	14.3 (−4.8 to 37.2)	36.0 (14.6 to 61.5)
SO_2					
Lag 0	9.1 (6.6 to 11.6)	5.5 (−5.5 to 17.8)	15.0 (2.1 to 29.6)	12.8 (0.7 to 26.3)	3.2 (−0.1 to 6.5)
Lag 1	2.7 (1.4 to 4.0)	5.6 (−0.3 to 11.9)	−0.2 (−6.2 to 6.3)	4.0 (−2.0 to 10.4)	0.3 (−1.2 to 1.9)
Lag 2	0.6 (−0.6 to 1.9)	4.2 (−1.8 to 10.6)	−3.9 (−10.0 to 2.6)	1.3 (−4.8 to 7.9)	−0.4 (−2.1 to 1.3)
Lag 3	0.9 (−0.1 to 1.8)	2.1 (−2.3 to 6.8)	−1.9 (−6.5 to 3.1)	1.7 (−2.9 to 6.4)	0.7 (−0.5 to 1.9)
Lag 4	1.5 (0.3 to 2.7)	0.2 (−5.6 to 6.3)	2.0 (−4.4 to 8.7)	2.1 (−4.0 to 8.5)	1.2 (−0.5 to 2.9)
Lag 5	0.8 (−0.3 to 1.9)	−1.1 (−6.5 to 4.7)	3.3 (−2.6 to 9.4)	−0.1 (−5.7 to 5.9)	2.1 (0.6 to 3.7)
Lag 6	−3.1 (−5.0 to −1.1)	−0.8 (−10.3 to 9.8)	−2.5 (−12.4 to 8.5)	−7.3 (−16.6 to 3.0)	2.2 (−0.6 to 5.1)
S 2 days	12.0 (1.5 to 23.5)	11.5 (−1.7 to 26.4)	14.8 (0.2 to 31.6)	17.3 (3.0 to 33.6)	3.5 (−0.1 to 7.2)
S 3 days	12.7 (1.2 to 25.4)	16.2 (1.4 to 33.1)	10.3 (−4.9 to 28.0)	18.8 (2.9 to 37.2)	3.1 (−0.6 to 7.0)
S 6 days	16.3 (0.7 to 34.3)	17.5 (−2.2 to 41.2)	14.0 (−6.6 to 39.1)	21.2 (−0.4 to 47.4)	7.3 (2.3 to 12.5)
S 7 days	12.7 (−3.0 to 30.9)	16.6 (−3.5 to 41.0)	11.1 (−9.5 to 36.4)	12.3 (−8.5 to 37.9)	9.7 (4.6 to 15.0)
CO					
Lag 0	−0.4 (−6.2 to 5.7)	−0.4 (−7.7 to 7.5)	−0.3 (−8.2 to 8.2)	−0.7 (−2.5 to 1.1)	1.5 (−6.5 to 10.2)
Lag 1	1.0 (−2.1 to 4.3)	2.9 (−1.2 to 7.2)	−0.5 (−4.7 to 3.8)	2.4 (1.4 to 3.4)	−0.7 (−4.9 to 3.6)
Lag 2	2.3 (−1.0 to 5.7)	3.5 (−0.9 to 8.0)	0.7 (−3.8 to 5.4)	3.0 (1.9 to 4.0)	0.2 (−4.3 to 4.9)
Lag 3	3.1 (0.6 to 5.7)	2.3 (−1.0 to 5.7)	2.5 (−0.9 to 6.0)	1.9 (1.2 to 2.7)	2.7 (−0.6 to 6.3)
Lag 4	3.2 (−0.1 to 6.6)	0.6 (−3.7 to 5.1)	4.0 (−0.3 to 8.6)	0.3 (−0.7 to 1.3)	5.4 (0.9 to 10.0)
Lag 5	2.2 (−0.9 to 5.5)	−0.6 (−4.7 to 3.7)	4.6 (0.4 to 8.9)	−0.9 (−1.9 to 0.0)	6.3 (2.0 to 10.8)
Lag 6	0.1 (−5.5 to 6.0)	−0.1 (−7.4 to 7.6)	3.2 (−4.3 to 11.2)	−0.9 (−2.5 to 0.8)	3.8 (−3.7 to 11.9)
S 2 days	0.6 (−6.1 to 7.7)	2.5 (−6.0 to 11.8)	−0.8 (−9.6 to 8.8)	1.7 (−0.4 to 3.9)	−1.4 (−10.1 to 8.0)
S 3 days	3.7 (−3.7 to 11.7)	6.1 (−3.5 to 16.6)	−0.1 (−9.6 to 10.3)	4.7 (2.4 to 7.2)	−0.1 (−9.5 to 10.2)
S 6 days	12.8 (2.2 to 24.6)	8.6 (−4.8 to 23.8)	11.3 (−2.0 to 26.4)	6.1 (2.8 to 9.5)	10.2 (−2.8 to 24.9)
S 7 days	12.9 (1.3 to 25.9)	8.4 (8.0 to 8.8)	14.8 (0.3 to 31.4)	5.2 (1.8 to 8.7)	14.3 (0.2 to 30.2)

*Sum.

Our findings are consistent with Sunyer *et al*,[10] who carried out one of the first time-series analyses of daily air pollution and daily ED admissions for COPD. They showed a linearly positive and significant relationship between air pollutants (SO_2, black smoke and CO) and ED visits for COPD in Barcelona, Spain. We expanded upon these findings with our data on NO_2 and its effects on the elderly. Another study, also conducted in Barcelona,[11] found that an increase of 25 μg/m³ in SO_2 increased the number of COPD-related ED visits by approximately 6% and 9% during winter and summer, respectively. Particulate pollution (as measured by black smoke) showed a similar association for the winter but was lower for the summer. For both pollutants, the effect was acute and higher at lag 1.

In terms of O_3, we found an acute impact at lag 0 in women despite the fact that other authors have reported more delayed associations between O_3 and COPD exacerbations. Tenías *et al*[12] showed that increases in O_3 (lag 5) and CO (lag 1) were associated with increases in the number of COPD-related ED visits in Valencia, Spain. The authors did not find associations with black smoke, NO_2 or SO_2. It is worth noting, however, that the Valencia study included adolescents and young adults.

A previous study carried out by our group in São Paulo[13] from 1996 to 1999 showed that the interquartile range increases in the 6-day moving average of SO_2 (11.82 μg/m³) and in the 4-day moving average of O_3 (35.87 μg/m³) increased the number of ED visits for lower airway chronic pulmonary diseases by 18% and 14%, respectively. In that study, however, only elderly participants were included and we did not use a stratified analysis. Moreover, ED visits included both COPD and asthma cases. In that study, we hypothesised that asthma exacerbations were mostly associated with changes in O_3 levels. In a pooled asthma–COPD analysis, Halonen *et al*[43] reported that the effects of gaseous and particulate matter differed by age group. This is despite the fact that they used different age groups from those in the present study.

In the Air Pollution and Health, a European Approach (APHEA) study, Anderson and co-workers[44] examined admissions for COPD in six European cities. The study suggested relationships between temporal trends in air pollutants and ED visits for COPD.[44] Reductions in SO_2, O_3, NO_2 and black smoke were accompanied by reductions in COPD-related ED admissions. The authors concluded that there was overwhelming evidence that air pollution, especially particulates, is associated

What is already known on this subject

- Respiratory infections are well-known triggers for chronic obstructive pulmonary disease exacerbations.
- The role of air pollutants remains underestimated.
- Investigations into the adverse effects of air pollutants on chronic obstructive pulmonary disease have been performed in different countries, but without emphasis on the effect modifiers by gender and age.

What this study adds

- This is the first study that evaluates the effects of air pollutants on chronic obstructive pulmonary disease-related emergency department visits stratified by gender and age.
- Air pollution should be considered a risk factor for chronic obstructive pulmonary disease exacerbations.
- The study shows that gender and age modify the magnitude and the lag structure of air pollutant effects on chronic obstructive pulmonary disease-related emergency department visits.
- The identification of a susceptible group reinforces the need for public policy measures to better control air pollution mainly in developing countries where effective procedures to reduce exposure to air pollution are still being implemented.

with exacerbations of COPD. It is important to note that the age of patients in these studies is, in its majority, around 65 years. Peel *et al*[14] found associations between increases in COPD-related ED visits and increases in NO_2 and CO. Both pollutants exhibited short-term effects.

Using a study design similar to ours, Ko *et al*[45] found associations between COPD-related hospital admissions and daily levels of particulates (PM_{10} and $PM_{2.5}$), SO_2, NO_2 and O_3 with longer lag structures and smaller size effects than those observed in São Paulo city.

Despite certain minor differences between our study and those mentioned above, all agree on one major point: urban air pollutants are hazardous to patients with COPD. The minor disagreements between age groups and pollutant-specific effects can most likely be attributed to study-specific design characteristics.

Studies in São Paulo have addressed the effects of air pollution on respiratory disease counts, mainly among children[46] and the elderly.[47] These and other studies have supported polices that have since been implemented by municipal, state and federal governments to reduce air pollution. When we examine specific disease groups, such as the group of patients with COPD that includes almost one million São Paulo inhabitants,[15] we are able to detect more problematic effects than those observed in the general population. We also note that these effects begin at lower pollution concentrations than those originally used to define air quality standards. Hence, we believe that this study may support efforts to limit air pollution emissions to stricter standards than those currently adopted in Brazil. In addition, despite the improvement in car engines and the consequent reduction in emissions, the number of cars has increased over the last decade, bringing more vehicles to the streets every day. Monitoring this scenario will require new studies that evaluate frail population groups and that analyse effect modifiers.

In conclusion, we identified a clear association between air pollution and daily COPD-related ED visits for individuals aged 40 years and older in the city of Sao Paulo, Brazil. Air pollution remains an underevaluated cause of COPD exacerbation. Besides infections, air pollution should be considered a risk factor for this outcome. Primary pollutants, which in São Paulo are generated mainly by cars, are among those factors that must be addressed in order to minimise the risks to public health.

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